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REMARKS

The present application was originally filed with 18 Claims. In a Restriction Requirement, the Examiner restricted the Claims into four Groups:

1) Group I contains Claims 1-15, directed to methods for combinatorial consensus mutagenesis;

2) Group II contains Claim 16, directed to a stabilized variant of beta-lactamase;

3) Group III contains Claim 17, directed to a stabilized variant of carcinoembryonic antigen binder; and

4) Group IV contains Claim 18, directed to a stabilized single chain fragment variable region.

Applicants elected the Claims in Group I (Claims 1-15), directed to methods for combinatorial consensus mutagenesis and reserved the right to file subsequent applications directed toward the remaining Groups.

In the present Office Action, the Examiner has made various rejections, set forth in the following order:

1) Claims 1-5 and 7-15 stand rejected under 35 USC §112, second paragraph, as allegedly being indefinite;

2) Claim 1 stands rejected under 35 USC §101, as allegedly being directed to non-statutory subject matter; and

3) Claims 1-5 and 10-15 stand rejected under 35 USC §102(b), as allegedly being anticipated by Crameri *et al.* (US Pat. No. 6,368,861).

1) The Claims are Definite

The Examiner has rejected Claims 1-5 and 7-15 under 35 USC §112, second paragraph, as allegedly being indefinite. In particular, the Examiner argues that the recitation of "combinatorial consensus library" is vague and indefinite. Applicants have amended Claim 1 to recite that the library is a combinatorial consensus mutagenesis library, as indicated in the preamble of the Claim as originally filed. In regard to Claim 3, Applicants submit that the screening is conducted on the enhanced combinatorial consensus library to identify at least one improved hit. As indicated in the definitions, "initial hits" are variants that are dentified by screening a combinatorial consensus mutagenesis library. In preferred embodiments, initial hits have improved performance characteristics, as compared to the starting gene. Likewise, as

indicated in the Specification, the term "improved hit" refers to a variant that was identified by screening an enhanced combinatorial consensus mutagenesis library (*See*, Specification at page 7, lines 17-19). Thus, there is no requirement that all of the variants generated in the method will be improved. Thus, the screening step is used to identify those variants that contain performance enhancing mutations. While Applicants respectfully submit that the Claim is clear, Claim 3 has been amended to indicate that the screening is conducted in order to identify improved hits that comprise performance-enhancing mutations. Applicants reserve the right to pursue the original and/or similar Claims in one or more subsequent applications. Applicants respectfully request that this rejection be withdrawn.

2) The Claims are Directed to Statutory Subject Matter

The Examiner has rejected Claim 1 under 35 USC §101, as allegedly being directed to non-statutory subject matter. In particular, the Examiner argues that there is no useful, concrete or tangible result. Applicants appreciate the Examiner's suggested Claim amendments. Applicants have amended the Claim to recite that the at least one initial hit is provided. Applicants respectfully submit that the Claim is directed toward statutory subject matter and request that this rejection be withdrawn.

3) The Claims are Novel

The Examiner has rejected Claims 1-5 and 10-15 under 35 USC §102(b), as allegedly being anticipated by Crameri *et al.* (US Pat. No. 6,368,861). In particular, the Examiner argues that Crameri *et al.* teach the various steps of the Claims. Applicants must respectfully disagree. Indeed, the claimed approach is essentially the inverse of the teaching of Crameri *et al.* The Crameri *et al.* methods use the homology alignments to identify shuffling primers to incorporate more diversity into their libraries. In contrast, by using the presently claimed method, the homology alignments are used to remove diversity—combinations of specific changes are created in the libraries that change one or more properties of the starting gene. Unlike the Crameri *et al.* method the useless residues are neglected in the presently claimed method. The Crameri *et al.* method includes all of the parts of the functional protein (*e.g.*, enzyme). In addition, more "junk segments" are incorporated by adding new sequences in each new step of gene shuffling. In contrast, the methods of the present invention are necessarily focused on a few useful amino acid segments.

In addition, the Crameri *et al.* method is iterative. The method is repeated with other genes, until the final molecule is identified. In contrast, in the presently claimed method, random libraries are generated first in order to obtain knowledge regarding the effect of single mutations via screening. The second round is only used to combine the best hits through random mutagenesis. Or, more simply, the first step is used to increase the knowledge useful in performing the second step. Applicants respectfully submit that the presently claimed methods are not taught nor even suggested by the Crameri *et al.* reference. Thus, Applicants respectfully submit that the Claims are novel and request that this rejection be withdrawn.

CONCLUSIONS

As all of the grounds of the Examiner's rejections have been addressed and in view of the above remarks, the Applicants believe the pending Claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner has any questions regarding the present application he or she is encouraged to contact the undersigned.

Respectfully submitted,

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